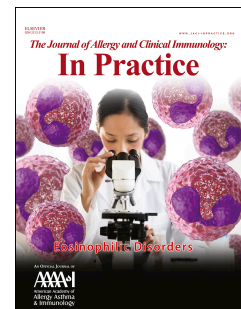


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Relieving Job: Dupilumab in Autosomal Dominant STAT3 Hyper-IgE Syndrome

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1 Relieving Job: Dupilumab in Autosomal Dominant STAT3 Hyper-IgE Syndrome

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40 **Access to Data and Data Analysis** Olga Staudacher and Horst von Bernuth had full access
41 to all the data in the study and take responsibility for the integrity of the data and the accuracy
42 of the data analysis.

43

44 **Conflicts of Interest**

45 Horst von Bernuth received honoraria for advisory boards from Takeda and for talks from
46 CSL-Behring. Susanne Lau received honoraria for advisory boards from Sanofi. Volker
47 Wahn received honoraria from CSL-Behring and the Plasma Protein Therapeutics
48 Association (PPTA) Germany. All other authors have no conflicts of interest to declare.

49

50 **Keywords:** Immunodeficiency – Hyper-IgE Syndrome - STAT3 – dupilumab - IL-4R α –
51 dermatitis - eczema

52

53 **Clinical Implication**

54 Control of dermatitis in autosomal dominant STAT3-Hyper-IgE Syndrome is an unmet clinical
55 need. We report on three children between 9 and 11 years of age with substantial relief
56 of HIES-related dermatitis under treatment with dupilumab, an antagonist of the IL-4-receptor- α -chain.
57

58 Clinical Communication

59 Autosomal dominant Hyper-IgE Syndrome (AD-HIES) was initially described as “Job’s
60 Syndrome”¹ and renamed due to high Immunoglobulin (Ig) E-levels.² Heterozygous
61 mutations in *STAT3* were identified as first genetic cause for AD-HIES.³ Patients exhibit 1)
62 pulmonary infections, mainly due to *Staphylococcus aureus* (*S. aureus*) and *Streptococcus*
63 *pneumoniae*, 2) bone brittleness and retention of decidual and delayed dentition of
64 permanent teeth, 3) dermatitis and skin infections with *S. aureus* and *Candida spp.*⁴ While
65 prophylaxis and treatment of infections has advanced, options for HIES-related dermatitis
66 are limited and consist of emollients, topical steroids and calcineurin-inhibitors.⁵ HIES-
67 related dermatitis resembles atopic dermatitis, caused both by an imbalance of Th2 over
68 Th1-cytokines, yet clinical presentation differs: HIES-related dermatitis may begin early
69 after birth and mainly affects head and extensor surfaces, while atopic dermatitis is absent
70 in neonates and displays an age dependent distribution pattern.¹⁻⁵ Data on the impact of
71 HIES-related dermatitis on quality of life (QoL) have not been published. In 11/2020, the
72 European Medicines Agency approved dupilumab for severe atopic dermatitis in children
73 between 6 -11 y/a. Dupilumab, a human monoclonal antibody, blocks the IL-4R α -chain
74 shared by IL-4 and IL-13 receptors. IL-4R α -chain expression is upregulated in patients
75 with dominant negative mutations in *STAT3*⁶ and there is preliminary evidence for
76 successful treatment of HIES-related dermatitis with dupilumab in adults.⁷⁻⁹ We here
77 report the control of HIES-related dermatitis with dupilumab in three children.

78

79 Patient 1, a nine-year-old boy, was diagnosed with AD-HIES caused by a mutation in *STAT3*
80 (c.21323C>G) at four years of age (y/a). Born prematurely (33+3), he suffered from
81 *Pneumocystis jirovecii* pneumonia at the corrected age of 2.5 months. An inborn
82 immunodeficiency was suspected and prophylaxis with cotrimoxazole initiated. Besides

83 growth being below the 3rd percentile for height, weight and head circumference, he suffers
84 from attention-deficit-hyperactivity-disorder. A persistent rash was present from birth, itching
85 was first noticed at 1 y/a. He developed chronic otitis externa at 3 y/a. Prior to dupilumab,
86 topical administration of mometasone and pimecrolimus were required to control eczema.
87 Despite topical medication, daily oral antihistamines and melatonin, constant pruritus
88 caused chronic sleeping difficulties.

89 Patient 2, an 11-year-old boy, has a family history of AD-HIES. The paternal mutation in
90 *STAT3* (V343L) was identified within two months after birth. Despite prophylaxis with
91 cotrimoxazole recurrent bacterial skin infections required intravenous anti-infective
92 treatment from the age of three months on. He developed a severe pneumonia with
93 subsequent pneumomediastinum and pneumatocele at 3 y/a. He was switched from
94 cotrimoxazole to prophylactic cephalexin after a cotrimoxazole-resistant *S. aureus* strain
95 was isolated from a nasal swab at 11 y/a. Dermatitis with severe itching was present since
96 early infancy. Topical mometasone could not control symptoms. Constant itch impaired
97 falling asleep.

98 Patient 3 is an 11-year-old boy with a history of neonatal pneumonia requiring ventilation for
99 two weeks and a severe “eczema toxicum infantum”. He was diagnosed with AD-HIES with
100 an underlying mutation in *STAT3* (R32Q) at two months of age. He suffered from recurrent
101 purulent otitis externa and media caused by *Pseudomonas aeruginosa* in his first years of
102 life, causing hearing impairment. He had five bone fractures without adequate trauma.
103 Prophylactic treatment with cotrimoxazole was discontinued because of resistant *S. aureus*
104 at 10 y/a. Local skin treatment, consisting of topical methylprednisolone aceponate and
105 pimecrolimus, was only occasionally applied (for summary of clinical characteristics see
106 table 1)..

107

108 Before treatment with dupilumab, informed consent was obtained. Initially, patients received
109 300 mg dupilumab subcutaneously every second week, followed by injections every 28
110 days. If symptom control was insufficient, treatment intervals were shortened to 21 days.
111 Total IgE was measured before starting therapy and after four months of therapy (Figure
112 E1). Severity of dermatitis by SCORing for Atopic Dermatitis (SCORAD) score, and QoL by
113 the questionnaires Children's Dermatology Life Quality Index (CDLQI) and Family
114 Dermatology Life Quality Index (FDLQI) were documented (Figure E2). Known adverse
115 events of dupilumab were explicitly asked for.

116 Upon introduction of dupilumab all parents reported reduced scratching. P1 slept through
117 the night for the first time; P2 fell asleep within "only" 30 minutes, resulting in an improved
118 attention span noticed by families and teachers. P1 was not able to fill out CDLQI, in both
119 other patients the score improved from 6 to 2. FDLQI dropped from 15 to 5, 18 to 6, and 10
120 to 3 in P1, P2, P3 respectively. SCORAD initially indicated moderate to severe dermatitis
121 (58-78) that improved to mild dermatitis in all patients already after four months of dupilumab
122 (5-15). On evaluation after four months only P1 reported intermittent itching and redness of
123 the eye. Treatment with a lubricating eye ointment reduced the discomfort. No other adverse
124 events were reported, particularly no infections. Treatment was continued after four months
125 in all patients due to the favorable outcome (Figure 1).

126 All patients reported suffered from moderate to severe HIES-related dermatitis (SCORADs
127 58 – 78). Dermatitis caused recurrent otitis externa with hearing impairment due to
128 obstruction of the external auditory canal and subsequent delay in speech development.
129 Pruritus lead to poor sleep quality, daytime tiredness and lack of focus at school. Parents of
130 all patients in this report had been well-trained in therapy of atopic dermatitis but were unable
131 to control HIES-related dermatitis. Aiming to achieve more efficient symptom control for
132 HIES-related dermatitis we initiated dupilumab in three children between 9 and 11 y/a. All

133 improved on dupilumab: all stopped topical corticosteroids, 2/3 patients, previously suffering
134 from chronic discharge of the ears, now reported dry ears. Improved sleep allowed
135 increased attention span at school. 2/3 patients showed recurrence of symptoms three
136 weeks after injections and thus increased the frequency of injections. No adverse events,
137 except for one episode of mild conjunctivitis, were reported. Treatment costs are higher for
138 dupilumab compared to conventional topical skin treatment. However, costs seem
139 warranted as attention spans and QoL improved substantially in our patients. Additionally,
140 HIES-related dermatitis improved markedly with a reduction of SCORAD scores over 50
141 points in all patients. We speculate that upon initiation of dupilumab physician visits,
142 antibiotic therapy and hospital stays, and treatments like speech therapy and vent tubes,
143 could be markedly reduced in further children with AD-HIES.

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146 **Figure legends**

147 **Table I.** Clinical baseline characteristics of three patients with autosomal dominant Hyper-
148 IgE Syndrome caused by heterozygous mutations in *STAT3*.

149

Figure 1. Improvement of dermatitis upon therapy with dupilumab in the face, on the ears and on extremities. State of the skin before therapy on is shown on the left, skin after four months of therapy with dupilumab (*) is shown on the right.

Table I

Patients characteristics			Genotype	Clinical phenotype		
Patient	Age	Sex	Mutation in <i>STAT3</i>	Infections	Other features	Skin
1	9 years	Male	c.21323C>G	Pneumocystis jirovecii pneumonia Chronic otitis	Delayed eruption of permanent teeth Scoliosis	Eczema
2	11 years	Male	V343L	Pneumonia with pneumatocele	Delayed eruption of permanent teeth	Eczema
3	11 years	Male	R32Q	Neonatal pneumonia Chronic otitis	Delayed eruption of permanent teeth Five fractured bones	Eczema

Repository Figure Legend

Figure E1. Panel with decrease of total IgE. Comparison before treatment with dupilumab and after four months of treatment. Dashed line = upper limit of normal.

Figure E2. Panels with Improvement of SCORAD and DFQLI. Comparison before treatment with dupilumab and after four months of treatment.

Fig. 1

